

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

15270C-09011PC

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22 JAN 2009

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|--|--|--|--|
| Applicant's or agent's file reference 15270C-19-11 | | FOR FURTHER ACTION See paragraph 2 below | |
| International application No. PCT/US 08/80370 | International filing date (day/month/year) 17 October 2008 (17.10.2008) | Priority date (day/month/year) 17 October 2008 (17.10.2008) | |
| International Patent Classification (IPC) or both national classification and IPC IPC(8) - A61K 38/00 (2008.04) USPC - 514/2 | | | |
| Applicant ELAN PHARMA INTERNATIONAL LIMITED | | | |

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

U-2209

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220. *8-17-10*

3. For further details, see notes to Form PCT/ISA/220.

| | | |
|---|---|--|
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201 | Date of completion of this opinion 22 December 2008 (22.12.2008) | Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774 |
|---|---|--|

Form PCT/ISA/237 (cover sheet) (April 2007)

*Undocketed
Transferred
Not Docketed
Abandoned*

Action: *Resp to Written Op.*
Due: *8-17-10*
By: *R45*

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/80370

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 the international application in the language in which it was filed.
 a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material
 on paper
 in electronic form
 - c. time of filing/furnishing
 contained in the international application as filed
 filed together with the international application in electronic form
 furnished subsequently to this Authority for the purposes of search
4. In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/80370

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

the entire international application
 claims Nos. 8, 10-17, 36-40, 104-115

because:

the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 8, 10-17, 36-40, 104-115 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 8, 10-17, 36-40, 104-115 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Note: claim 8 fails to claim multiple dependency in the alternative.

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

no international search report has been established for said claims Nos. 8, 10-17, 36-40, 104-115

a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/80370

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|--------|---|-----|
| Novelty (N) | Claims | 3-4, 9, 18-35, 41-56, 60, 74-75, 95-103 | YES |
| | Claims | 1-2, 5-7, 57-59, 61-73, 76-94 | NO |
| Inventive step (IS) | Claims | None | YES |
| | Claims | 1-7, 9, 18-35, 41-103 | NO |
| Industrial applicability (IA) | Claims | 1-7, 9, 18-35, 41-103 | YES |
| | Claims | None | NO |

2. Citations and explanations:

Claims 1-2, 5-7, 57-59, 61-73, and 76-94 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0193850 A1 to Warne et al. (hereinafter "Warne").

As to claim 1, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg (para [0035]), wherein the antibody specifically binds to beta amyloid peptide (A-beta) with a binding affinity of at least 10e7 M-1 (para [0059]), and thereby therapeutically treat the patient (para [0036]).

As to claim 2, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg (para [0035]), wherein the antibody specifically binds to an N-terminal fragment of beta amyloid peptide (A-beta) with a binding affinity of at least 10e7 M-1 (para [0059], [0127]), and thereby therapeutically treat the patient (para [0036]).

As to claims 5-7, Warne teaches that the antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under PTA-5130 (para [0010], [0129]). Although Warne does not expressly teach that the antibody is bapineuzumab, the antibody produced by the hybridoma PTA-5130 is inherently bapineuzumab.

As to claims 57-59, Warne teaches a method of treating Alzheimer's disease (para [0036], [0050]), comprising: administering to a patient having the disease (para [0036]) an antibody that specifically binds to an N-terminal fragment of A-beta (para [0127]) in a regime sufficient to maintain an average serum concentration of the antibody in the patient of 1 ug antibody/ml serum (para [0173]), thereby treating the patient (para [0036]).

As to claim 61, Warne teaches that the antibody is administered intravenously (para [0098]).

As to claims 62-63, Warne teaches that a dose of 0.1-1.0 mg/kg or 0.5-1.0 mg/kg (para [0172]) is administered monthly (para [0173]).

As to claim 64, Warne teaches that the antibody is administered subcutaneously (para [0035]).

As to claim 65, Warne teaches that the antibody is administered at a frequency between weekly and monthly (para [0172]).

As to claim 66, Warne teaches that the antibody is administered weekly (para [0173]).

As to claims 67-73, Warne teaches that the antibody is administered at a dose of 0.10-0.35 mg/kg, 0.05-0.25 mg/kg, 0.015-0.2 mg/kg, 0.05-0.15 mg/kg, 0.05-0.07 mg/kg, 0.06 mg/kg, 0.1-0.15 mg/kg (para [0172]) weekly to biweekly (para [0172]-[0173]).

As to claim 76, Warne teaches measuring the concentration of antibody in the serum and adjusting the regime if the measured concentration falls outside the range (para [0173]).

As to claims 77-86, Warne teaches a method of treating Alzheimer's disease (para [0036], [0050]), comprising: subcutaneously administering to a patient having the disease (para [0035]-[0036]) an antibody that specifically binds to an N-terminal fragment of A-beta (para [0127]), wherein the antibody is administered at a dose of 0.01-0.6 mg/kg, 0.05-0.5 mg/kg, 0.05-0.25 mg/kg, 0.015-0.2 mg/kg, 0.05-0.15 mg/kg, 0.05-0.07 mg/kg, 0.06 mg/kg, 0.1-0.15 mg/kg, 0.1-0.3 mg/kg, or 0.2 mg/kg (para [0172]) and a frequency of between weekly and monthly, weekly to biweekly, or monthly (para [0172]-[0173]).

----- (Continued in Supplemental Box) -----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/80370

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2. Citations and Explanations:

As to claim 87-94, Warne teaches a method of treating Alzheimer's disease (para [0036], [0050]), comprising: subcutaneously administering to a patient having the disease (para [0035]-[0036]) an antibody that specifically binds to an N-terminal fragment of A-beta (para [0127]), wherein the antibody is administered at a dose of 1-40 mg, 5-25 mg, 2.5-15 mg, 1-12 mg, 2.5-10 mg, 2.5-5 mg, 4-5 mg, or 7-10 mg (para [0174], [0176]) and a frequency of between weekly and monthly or weekly-biweekly (para [0172]-[0173]).

Claims 60, 74-75, and 95-103 lack an inventive step under PCT Article 33(3) as being obvious over Warne.

As to claim 60, Warne teaches a method of treating Alzheimer's disease (see explanation above for claim 57). Warne does not teach that the average serum concentration of is within a range of 2-4 ug antibody/ml serum. However, Warne teaches that the serum concentration is 1-1000 ug/ml (para [0173]), and it would have been obvious to one of skill in the art that the preferred serum concentration could fall anywhere in that range, including between 2-4 ug/ml.

As to claims 74-75, Warne does not teach that the average serum concentration of the antibody is maintained for at least six months or at least one year. However, it would have been obvious to one of skill in the art to maintain the average serum concentration of the antibody for such extended periods of time, because it would have been necessary to treat a chronic, progressive disease such as Alzheimer's disease.

As to claims 95-103, Warne teaches a method of treating Alzheimer's disease (para [0036], [0050]), comprising: administering to a patient having the disease (para [0036]) an antibody that specifically binds to an N-terminal fragment of A-beta (para [0127]) in a regime sufficient to maintain a serum concentration of the antibody in the patient of 1-1000 ug antibody/ml serum (para [0173]) and thereby treating the patient (para [0036]). Warne does not expressly teach that the maximum or average serum concentration of antibody is less than about 28 ug/ml, within a range of about 4-28 ug/ml, 4-18 ug/ml, below about 7 ug/ml, within a range of 2-7 ug/ml, or about 5 ug/ml. However, it would have been obvious to one of skill in the art that the preferred serum concentration could fall anywhere in the disclosed range of 1-1000 ug/ml, including any of the recited ranges.

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over Warne in view of US 2007/0082367 A1 to Godavarti et al. (hereinafter "Godavarti").

As to claim 9, Warne teaches a method of therapeutically treating Alzheimer's disease, wherein the antibody is a humanized antibody (see explanation above for claim 5). Warne further teaches that the humanized antibody is a humanized version of mouse antibody 12A11 (para [0010]). Warne does not teach that the antibody is expressed by the hybridoma deposited under ATCC under PTA-7271. Godavarti teaches a hybridoma expressing a humanized version of mouse antibody 12A11 deposited under ATCC under PTA-7271 (para [0137]-[0138]). It would have been obvious to one of skill in the art to use an antibody expressed by the hybridoma PTA-7271, because it would have been obvious to use a humanized 12A11 antibody from any known source.

Claims 18-20 and 23-26 lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of US 2006/0121038 A9 to Schenk et al. (hereinafter "Schenk").

As to claims 18 and 23, Warne teaches a method of therapeutically treating Alzheimer's disease (see explanation above for claim 1). Warne does not teach further monitoring the patient by at least one type of assessment selected from the recited assessments. Schenk teaches the use of the Mini-Mental State Exam (MMSE) to monitor Alzheimer's disease patients during therapeutic treatment with an antibody to A-beta (para [0008], [0408]-[0409]). It would have been obvious to use the MMSE to monitor the patients being treated using the method taught by Warne, because one of skill in the art would have known that the MMSE is routinely used to monitor Alzheimer's disease patients during therapy, including therapy with an A-beta antibody as taught by Schenk.

As to claim 19, Schenk teaches that the assessment type is an Alzheimer's Disease Assessment Scale (ADAS) (para [0408]). Although Schenk does not teach that the assessment type is the ADAS-cognitive (ADAS-COG), it would have been obvious to one of skill in the art to perform well-known subtypes of known assessments, including ADAS-COG, as such subtypes were routinely used to monitor Alzheimer's disease.

As to claims 20 and 24, Schenk teaches that the monitoring is administered on multiple occasions (para [0409]).

----- (Continued in Supplemental Box) ----- ==

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/80370

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2. Citations and Explanations (first Supplemental Box):

As to claim 25, Schenk teaches that the MMSE is performed before administering the dosage and 6 months after administering the dosage (para [0409]), but does not teach that the MMSE is administered at week 4, week 16, or 1 year after administering the dosage. However, Schenk teaches that the monitoring is performed at least every six months (para [0409]), which implies that the monitoring is probably performed 1 year after administering the dosage (i.e., after two iterations of 6 months). It further would have been obvious that the monitoring could be performed more often ("at least" every six months implies it may be done with higher frequency), and one of skill in the art would have determined that week 4 and week 16 were desirable times to monitor via routine experimentation.

As to claim 26, Schenk does not teach that the MMSE score measured after administration is higher than a previously assessed MMSE score. However, it would have been obvious to one of skill in the art that achieving a higher score would be a desirable result of therapeutic treatment.

Claims 3-4, 27, 29-31, 33-34, 41-42, and 45-56, lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of the article entitled "A case of reversible posterior leukoencephalopathy syndrome after rituximab infusion" by Mavragani et al. (hereinafter "Mavragani"), and further in view of the article entitled "Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer" by Allen et al. (hereinafter "Allen").

As to claim 3, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody that specifically binds to an N-terminal fragment of beta amyloid peptide (A-beta) with a binding affinity of at least 10⁸ M-1 (para [0059], [0127]). Warne does not teach monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema. Mavragani teaches that PRES (also referred to as "reversible posterior leukoencephalopathy syndrome" or "RPLS") is a side effect of administration of the monoclonal antibody rituximab (pg 1450, para 1, 6, 8). Allen teaches that PRES (RPLS) is a side effect of administration of the monoclonal antibody bevacizumab (abstract). Both Mavragani (pg 1451, para 3) and Allen (pg 1477, para 3) speculate that the RPLS is related to the antigen-binding specificity of the respective antibodies. However, one of skill in the art would have recognized that the same side effect in two different antibodies might be due to a generic side effect associated with administration of monoclonal antibodies regardless of binding specificity. Accordingly, it would have been obvious to one of skill in the art that PRES might be a potential side effect of administration of an antibody to A-beta, and it would have been obvious to monitor the patient for PRES, because it was routine in the art to monitor patients receiving medical treatment for expected side effects.

As to claim 4, Warne teaches a method of therapeutically treating Alzheimer's disease (para [0036], [0050]), comprising administering by intravenous infusion to a patient suffering from the disease (para [0036], [0098]) a dosage of an antibody within a range of about 0.5 mg/kg to less than 5 mg/kg (para [0035]), wherein the antibody specifically binds to an N-terminal fragment of beta amyloid peptide (A-beta) with a binding affinity of at least 10⁸ M-1 (para [0059], [0127]). Warne does not teach monitoring the patient for posterior reversible encephalopathy syndrome (PRES) or vascular edema. However, it would have been obvious to one of skill in the art to do so, for the same reasoning given above for claim 3.

As to claim 27, Mavragani teaches that the monitoring comprises performing an MRI scan (pg 1450, para 6).

As to claims 29-30, Mavragani teaches that the monitoring comprises identifying at least one clinical symptom associated with PRES, such as headache, visual abnormalities, and seizures (pg 1451, para 1).

As to claims 31, 33, and 41 Mavragani does not teach reducing or suspending the dosage based on an outcome of the MRI scan that is indicative of PRES or vascular edema, or the identification of at least one clinical symptom associated with PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse side effects.

As to claim 34, Mavragani does not teach that the MRI scan is every 3 months, every 6 months, or every year. However, it would have been obvious to one of skill in the art to perform the monitoring at such intervals in order to monitor the progress of the treatment over time, and one of skill in the art would have determined the appropriate intervals at which to perform the MRI scan via routine experimentation.

As to claim 42, Mavragani teaches that the at least one clinical symptom associated with PRES is headache, visual abnormalities, or seizures (pg 1451, para 1).

—(Continued in Supplemental Box)—

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/0370

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2. Citations and Explanations (second Supplemental Box):

As to claims 45-46, Mavragani does not teach that the monitoring indicates presence of PRES or vascular edema at a first time point after administration, and absence of PRES or vascular edema at a second time point after the first time point, and the patient is administered a first dosage before the monitoring indicates presence of PRES or vascular edema, a second dosage or no dosage after the monitoring detects presence of PRES or vascular edema, and a third dosage after the monitoring detects absence of PRES or vascular edema, wherein the first and third dosage are higher than the second dosage. However, such a scenario would have been obvious to one of skill in the art, because it was routine in the art to reduce the dosage after the manifestation of an adverse side effect (i.e., after the first dosage), and then to increase it again (e.g., the same dosage as the first dosage) in a subsequent dosage in order to determine whether the initial manifestation of the side effect was real or an artifact.

As to claims 47-49, Warne teaches that the antibody is a humanized version of mouse antibody 3D6 expressed by the hybridoma deposited under ATCC under PTA-5130 (para [0010], [0129]). Although Warne does not expressly teach that the antibody is bapineuzumab, the antibody produced by the hybridoma PTA-5130 is inherently bapineuzumab.

As to claim 50 and 53, Mavragani teaches that the PRES is determined using an MRI scan (pg 1450, para 6), but does not teach that the antibody is administered at a first dosage before PRES or vascular edema is determined from the MRI scan and a second dosage after PRES or vascular edema is determined from the MRI scan, and the second dosage is less than the first dosage. However, it would have been obvious to one of skill in the art to administer the antibody (e.g., bapineuzumab) as recited, because it was routine in the art to reduce the dosage of a therapeutic agent after the manifestation of an adverse side effect.

As to claims 51-52 and 54-55, Warne teaches that the preferred dosage of the antibody such as bapineuzumab may be 3-5 mg/kg or 0.5-3 mg/kg (para [0035]). Although Warne does not teach a preferred first and second dosage, including wherein the second dosage is half of the first dosage, methods for determining the appropriate dosage were routine in the art, and one of skill in the art would have arrived at the appropriate dosage via routine experimentation.

As to claim 56, Warne teaches a kit for the treatment of Alzheimer's (para [0033]), comprising:

- (a) a glass vial (para [0035]) containing a formulation comprising:
 - (i) about 10-250 mg of a humanized anti-A-beta antibody (para [0035]),
 - (ii) about 4% mannitol or about 150 mM NaCl (para [0035]),
 - (iii) about 5-10 mM histidine (para [0035]), and
 - (iv) about 10 mM methionine (para [0035]); and
- (b) instructions for use (para [0033]).

Warne does not teach that the instructions are to monitor a patient to whom the formulation is administered for PRES or vascular edema. However, it would have been obvious to one of skill in the art to monitor the patient for PRES, for the same reasoning given above for claims 3-4, and it therefore would have been obvious to one of skill in the art to include instructions for monitoring for PRES, because it was routine in the art to include instructions with kits relating to the use of their components and any adverse side effects that might be produced.

Claims 21-22 lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of Schenk, and further in view of US 20060234912 A1 to Wang et al. (hereinafter "Wang").

As to claims 21, Warne in view of Schenk teaches a method of therapeutically treating Alzheimer's disease (see explanation above for claim 18). Neither Warne nor Schenk teaches that the assessment type is a Neurological Test Battery (NTB). Wang teaches the use of an NTB to monitor sensory and motor function (para [0159]). It would have been obvious to one of skill in the art to use an NTB to monitor an Alzheimer's disease treatment, because Wang teaches that the NTP is "standard" for monitoring sensory and motor function (para [0159]), and it would have been obvious that sensory and motor function may be affected in a neurological disorder such as Alzheimer's disease and should be monitored to determine the efficacy of treatment.

As to claim 22, Schenk teaches that the monitoring is administered on multiple occasions (para [0409]).

Claims 28, 32, 35, and 43-44 lack an inventive step under PCT Article 33(3) as being obvious over Warne in view of Mavragani, further in view of Allen, and further in view of US 2006/0182321 A1 to Hu et al. (hereinafter "Hu").

As to claim 28, Warne in view of Mavragani and Allen teaches a method of therapeutically treating Alzheimer's disease (see explanation above for claim 27). Neither Warne, Mavragani, nor Allen teaches that the monitoring further comprises performing a FLAIR sequence imaging. Hu teaches the use of a FLAIR sequence imaging to monitor the brain of a patient such as an Alzheimer's patient as part of an MRI (para [0002], [0005], [0009], [0042]). Accordingly, it would have been obvious to one of skill in the art that any known type of MRI, including a FLAIR sequence imaging, could provide a method for monitoring an Alzheimer's patient during therapeutic treatment.

(Continued in Supplemental Box)-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/80370

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2. Citations and Explanations (third Supplemental Box):

As to claim 32, Wang does not teach reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse side effects.

As to claim 35, Wang does not teach that the FLAIR sequence imaging is every 3 months, every 6 months, or every year. However, it would have been obvious to one of skill in the art to perform the monitoring at such intervals in order to monitor the progress of the treatment over time, and one of skill in the art would have determined the appropriate intervals at which to perform the MRI scan via routine experimentation.

As to claims 43-44, Mavragani teaches that the monitoring comprises identifying at least one clinical symptom associated with PRES, such as headache, visual abnormalities, and seizures (pg 1451, para 1), but does not teach reducing or suspending the dosage based on an outcome of the FLAIR sequence imaging that is indicative of PRES or vascular edema and identification of at least one clinical symptom associated with PRES or vascular edema. However, it would have been obvious to one of skill in the art to do so, because it was routine in the art to reduce or suspend a therapeutic treatment upon the manifestation of adverse side effects.

Claims 1-7, 9, 18-35, 41-103 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.